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REVIEW

Basement membrane components are key players in specialized extracellular matrices

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Abstract More than three decades ago, basement membranes (BMs) were described as membrane-like structures capable of isolating a cell from and connecting a cell to its environment. Since this time, it has been revealed that BMs are specialized extracellular matrices (sECMs) with unique components that support important functions including differentiation, proliferation, migration, and chemotaxis of cells during development. The composition of these sECM is as unique as the tissues to which they are localized, opening the possibility that such matrices can fulfill distinct functions. Changes in BM composition play significant roles in facilitating the development of various diseases. Furthermore, tissues have to provide sECM for their stem cells during development and for their adult life. Here, we briefly review the latest research on these unique sECM and their components with a special emphasis on embryonic and adult stem cells and their niches.

Keywords Basement membrane · Stem cell niche · Epithelial mesenchymal transition · Cancer · Review

Introduction

The extracellular matrix (ECM) provides a chemical and mechanical structure, which is essential for development and for responses to (patho)-physiological signals [1]. Differentiation and cell fate decisions are controlled by their surrounding microenvironment of which the ECM is one of the main constituents [2]. The diverse characteristics of the ECM, such as stiffness and composition, have been recognized as being responsible for the variation of cellular behavior involving an individual's health [3, 4].

Basement membranes (BMs) are highly specialized extracellular matrices (sECMs) forming thin acellular layers that underlie cells and separate the cells from and connect them to their interstitial matrix [5]. The formation of BMs is a prerequisite for normal tissue development and function [6, 7]. In addition, individual components of BMs regulate different biological activities, such as the development, proliferation, differentiation, growth, and migration of cells, via cell surface receptors (mostly integrins) and non-integrin-receptors [8]. Furthermore, BMs control cellular functions by binding and modulating the local concentrations of growth factors and cytokines [4, 9]. BMs are able to regulate cell polarity [10, 11], cell adhesion, spreading, and migration via their effects on the cytoskeleton [12–14]. Adult tissues need a highly selective sECM to maintain their stem cell properties particularly in stem cells during development [15, 16] and it has been shown that BMs have been implicated in niche function [17].

BMs are made of diverse extracellular matrix molecules depending on the tissue in which they are localized. Due to the discovery of new components and isoforms, the complexity of BM composition has been considerably increased, providing an impressive number of tissue- and site-specific BMs [18]. The ability of BMs to adapt to changing cell biological requirements is dependent on how the components are deposited and arranged inside the matrix (for review, see [14, 19]). The deposition of BM components is also dependent on aging, as has been demonstrated using mouse retina and cartilage tissue [20, 21]. BM components can also be localized in the ECM, independent of the typical membrane-like structures seen

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in electron microscopy. Recently, it has been shown that BM components are found in the pericellular matrix of human and murine cartilage and osteoarthritis disease [21–23]. In the lymph nodes, BM components are deposited outside a BM structure [5]. Changes in the qualitative or quantitative composition, localization, or structure of BM proteins have been shown to be involved in the development of different disease states as discussed in detail below.

Herein, we want to briefly introduce the ubiquitous components of the BM including laminins, perlecan, collagen IV, nidogen-1, and nidogen-2 [5], with emphasis placed on their variable tissue distributions. We will further discuss the role of BM components and their uniqueness in different stem cell niches.

Ubiquitous BM components at a glance

Excellent detailed reviews regarding these unique matrix proteins and receptors, such as integrins, have just recently been published and the reader is directed to these reviews for comprehensive information [4, 14, 24–33]. An overview can be found in Table 1.

Laminins

Laminins are heterotrimeric glycoproteins, which are composed of three chains including one α, one β, and one γ chain. Five alpha, four β, and three γ chains exist, and in vertebrates, these chains can assemble into at least 16 [25] different isoforms [14, 34]. These isoforms are differentially distributed during development and in adult tissues, thereby fulfilling specific functions as key regulators of tissue structure and cell behavior [35]. In general, laminin-111 and laminin-511 are the main laminins required during embryonic development (Fig. 1a, b), whereas other laminins have been identified as being important for organ maturation and specific tissue functions [26]. For instance, laminin-211 and laminin-221 are mainly found in skeletal muscle [36, 37]. Laminin-221, -421 and -521 are localized to the neuromuscular junction and coordinate postsynaptic with presynaptic maturation [38]. Laminin-511 is the major laminin in ectodermal BM and in most epithelium including the skin, kidney, and lung to name a few. Laminin-332 plays a major role in skin function [39]. Furthermore, laminin-332 has been previously shown to be transiently expressed in embryonic cartilage [40]. Laminin-111 has been observed in the chondrocytes of healthy human cartilage especially that which is localized to the superficial layer [41] where the mesenchymal progenitor cells are localized [42, 43]. In the vasculature, laminin-411, -421, -511 and -521 can be found. Although this laminin deposition appears to be significantly varied, the tissue distribution of laminins is mainly dependent on the expression of its alpha subunits, though the mechanisms are not yet fully understood [25]. However, it is well known that alpha subunits and their specific interaction with integrins or non-integrin receptors are essential for the self-assembly and polymerization of laminin networks. This network assembling is a prerequisite for basement membrane formation [25, 26]. To name just a few laminin-receptor specificities, α-dystroglycan presumably binds laminin α1 and α2 chains, whereas the Lutheran blood group glycoprotein binds only laminin α5 chains. Integrins such as $\alpha3\beta1$, $\alpha6\beta1$ and $\alpha6\beta4$ can regulate the deposition of laminin-332 in keratinocytes [14] and interact with laminin α5 chains [26]. Further integrin receptors for laminins are known as the $\alpha1\beta1$, $\alpha2\beta2$, $\alpha7\beta1$ (via laminin α2), $\alpha9\beta1$, and $\alpha v\beta3$ (via laminin α4) receptors, as well as the non-integrin receptor syndecans [25].

It has been demonstrated by immunogold electronmicroscopy that laminin-111 is oriented differently inside the BM of the same tissue, for tissues such as the proximal and distal tubule (Fig. 1c, d) of the murine kidney [44]. Furthermore, laminin-211 and -221 that are located in Schwann cells are deposited in mesh-like structures for organizing the receptors and cytoskeletal elements [45], whereas a fibrillar network, for example, of laminin-311 in the lung seems ideal for the transmission of mechanosignals such as stretch [46]. The pattern and stabilization of laminins is further influenced by other BM components, such as nidogens or perlecan [14]. Moreover, the deposition pattern of laminin-332 has been shown to vary for non-migratory and migratory keratinocytes in vitro. While non-motile cells revealed a rosette-like pattern of laminin-332 in their matrix, motile cells assembled trails for migration [13]. Under physiological or pathological conditions (e.g., metastasis), fragments of laminins not able to polymerize into networks are deposited into the ECM, thereby stimulating cell migration as shown for laminin-332 [47–49].

According to the functions of laminins in BMs, it should be mentioned that the ability of laminin subunits to accumulate into heterotrimers and further assemble networks is absolutely required for the initial BM assembly [26]. In *Drosophila*, it has been shown that the complete absence of laminin leads to the complete absence of BMs resulting in a disorganized ECM and an abnormal accumulation of major BM components. Organ and tissue development is subsequently prevented in the gut, muscle and nervous system [50]. The important functions of laminin isoforms in tissues can further be demonstrated by analysis of knockout mice or of various mutations in mice, which also resemble human diseases. Most laminin subunit knockouts are lethal, such as laminin γ1 [7], due to the lack of BM formation [25]. If the mice survive, they develop severe diseases,

Table 1 Overview of BM components in specialized ECMs (mentioned in the text)

BM isoform	Interactive receptors/ligands	Site of expression	Phenotypes of deficient mice	Involvement in human diseases
Laminin-111	Lam α1: α-dystroglycan	Development, ubiquitously in BMs, adult articular cartilage	Lam γ1: lethal	
Laminin-211	Lam α2: α7β1, α-dystroglycan	Skeletal muscle, schwann cells, eye (limbal compartment)	Lam α2: congenital muscular dystrophy	Congenital muscular dystrophy
Laminin-221		Skeletal muscle, schwann cells, neuromuscular junction	Lam β2: defective, disorganized neuromuscular junctions	Pierson syndrome
Laminin-332	Lam α3: α3β1, α6β1, α6β4	Skin, embryonic cartilage	Severe skin blistering disease	Epidermolysis bullosa Fragments: cancer/ metastasis
Laminin-411	Lam α4: αvβ3	Vasculature	Lam α4: hemorrhaging, cardiomyopathy	Inflammation Lam α4 increased in cancer/metastasis
Laminin-421		Vasculature, neuromuscular junction		
Laminin-511	Lam α5: Lutheran Bloodgroup glycoprotein, B-CAM, α3β1, α6β1, α6,β4	Development, vasculature, epithelium	Lam α5: impaired hair follicle, teeth growth and development, defective glomerulogenesis	Lam α5 decreased in cancer/metastasis
Perlecan	Interaction with and support of diverse growth factors	Ubiquitously in BMs, articular cartilage, growth plate	SJS: chondrodysplasia, myotonia, short stature DDSH: lethal, chondrodysplasia, exencephaly, abnormal heart development, absence of acetylcholinesterase at neuromuscular junction	SJS, DDSH (lethal) Osteoarthritis, cancer/metastasis
Collagen IV-(112)	α1β1, α2β1	Development, ubiquitously in BMs	Lethal	Collagen IV α1: HANAC syndrome, encephaloclastic porencephaly, recurrent hemorrhagic stroke
Collagen IV-(345)	α3β1, α6β1, α10β1, α11β1, αvβ3, CD44, DDR-1	Kidney, inner ear (cochlea), eye, testis, lung	Collagen IV α3, α4 or α5 → Alport syndrome: progressive renal failure/fibrosis, disrupted glomerular BM, deafness and retinopathy, lethal	Alport syndrome Goodpasture syndrome
Collagen IV-(556)		Bowman′s capsule (kidney), skin, esophagus, smooth muscle cells, synovia (knee)		Every collagen IV isoforms as fragments: metastasis (?)

Table 1 continued

BM isoform	Interactive receptors/ligands	Site of expression	Phenotypes of deficient mice	Involvement in human diseases
Nidogen-1	$\alpha v\beta 3$, $\alpha 3\beta 1$, Laminin $\gamma 1$, collagen IV, perlecan, fibronectin, collagen I, collagen II	Ubiquitously in BMs, limb development, rib anlagen, adult articular cartilage	Single: neurological defects, epilepsy, structural alterations in brain capillaries and lens capsule, impaired wound healing	Osteoarthritis, metastasis (?)
Nidogen-2	Laminin, collagen IV, perlecan, fibronectin, collagen I, collagen II	Like nidogen-1, but more restricted in muscle, neuromuscular junction and cartilage	Single: no phenotype Both nidogens: lethal, syndactyly, lung and heart abnormalities, microhemorrhaging of skin	Osteoarthritis Ovarian cancer (biomarker?)

Lam Laminin, *SJS* Schwartz-Jampel-syndrome, *DDSH* dyssegmental chondrodysplasia of the Silverman-Handmaker-Type, *HANAC* hereditary angiopathy with nephropathy, aneurysm and muscle cramps

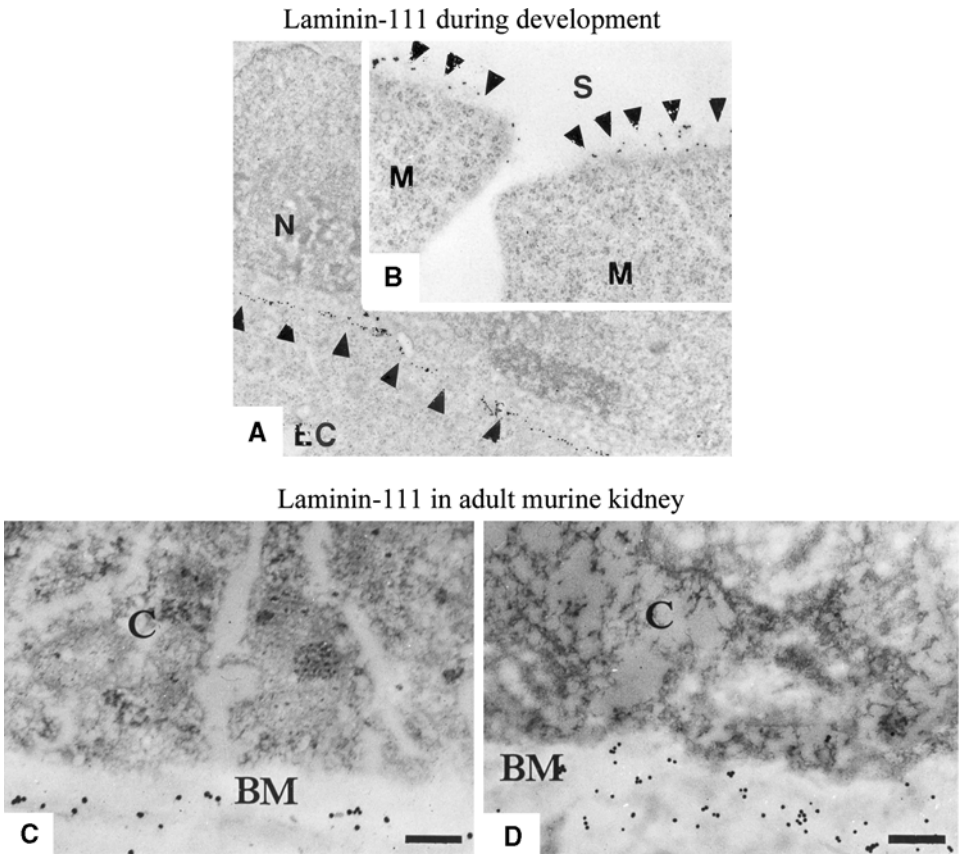

Fig. 1 Laminin-111 is found in the very early mouse embryo, here shown at day 6, even before a proper BM has assembled (**a**) and in BM remnants of migrating mesodermal cells (**b**) at day 7. *M* Mesodermal cell, *N* nucleus, *S* mesodermal space, *EC* ectodermal cell. (Taken from [200], with permission from the publisher). In adult murine kidney, the tail (formerly the E8 domain) of laminin-111 is orientated towards the lamina fibroreticularis in the basement membrane of the proximal tubule (**c**), while the molecule is randomly distributed in the distal tubule (**d**). *C* Cell, *BM* basement membrane. (Taken from [44], with permission from the publisher)

according to the subunits and their tissue distributions. Laminin α2 deficiency, known to affect humans, causes congenital muscular dystrophy [51], while laminin $\beta 2$ deficiency, known in humans as Pierson syndrome, results in disorganized and defective neuromuscular junctions [52, 53]. Laminin α5 deficiency causes impaired hair follicle, teeth growth and development issues [54] as well as defective glomerulogenesis [55]. Laminin-332 mutations are related to epidermolysis bullosa, a severe skin blistering disease [56, 57], while laminin α4 mutations cause hemorrhaging and cardiomyopathy [58]. Furthermore, laminins are known to be involved in cancer development and metastasis [48]. Additionally, laminins have been shown to play a role in the growth and/or differentiation of embryonic and adult stem/progenitor cells, which will be discussed in detail below.

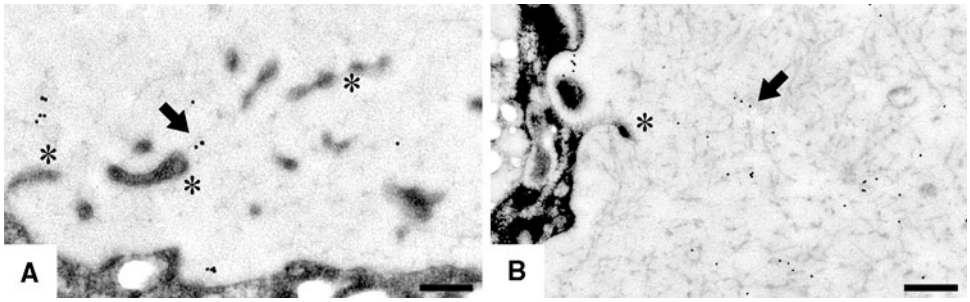

Fig. 2 Perlecan is found in the pericellular matrix next to a healthy chondrocyte (**a**) and increased amounts next to an elongated chondrocyte (**b**) from osteoarthritic tissue. (Taken from [23], with permission from the publisher)

Perlecan

Perlecan is a proteoglycan composed of five domains, and like laminins, has the ability to self-assemble into oligomers [59]. Structurally, perlecan exhibits potential sites for glycosaminoglycan-(GAG)-chains proximal to its protein core like heparan sulfate (HS) and chondroitin sulfate (CS). Both the protein core and the GAG-chains are able to interact with diverse ECM molecules including all the main BM components, growth factors and receptors [28, 29], thereby initiating and controlling the migration, proliferation and differentiation of different cells by mediating cell signaling events. As typical for proteoglycans, perlecan mediates these functions by mainly controlling growth factor signaling and activation of fibroblast growth factors (FGFs), bone morphogenic proteins (BMPs), platelet-derived growth factor (PDGF), vascular endothelial growth factors (VEGFs), transforming growth factors (TGFβs), epithelial growth factor (EGF), hepatocyte growth factor (HGF), and insulin-like growth factor (IGF) [28, 59–62].

Perlecan is important in the developmental processes [63] that occur during angiogenesis [64], anti-angiogenesis [65], cardiovascular development [66], neurogenesis [67], and chondrogenesis [68]. Although there is only one perlecan, tissue-dependent structural differences have been reported [28, 68]. The GAG-chains can vary between different tissues enabling perlecan to fulfill tissue-specific functions, such as significant amounts of HS-chains that are important for endothelial cells and angiogenesis [28]. However, in articular cartilage, particularly high amounts of CS-chains are found. The GAGs of perlecan play crucial roles in the differentiation potential of cells [69]. Interestingly, these cartilage-specific perlecan CS-chains are also able to influence ECM by stimulating collagen fibril formation [70]. Furthermore, a fragment of perlecan, endorepellin (domain V of perlecan), has anti-angiogenic functions due to integrin $\alpha 2\beta 1$ and is thought to be a potentially useful tool in future cancer therapy [71].

Mutations, resulting in reduced perlecan, resembles Schwartz-Jampel syndrome (SJS) in humans [72, 73]. Patients develop skeletal chondrodysplasia and myotonia and are characterized by short stature. Moreover, a total knockout of perlecan in humans and mice results in dyssegmental chondrodysplasia of the Silverman-Handmaker type (DDSH) and early lethality due to respiratory distress [74]. A severe chondrodysplasia, ex- or microencephaly, abnormalities in heart development and the absence of acetylcholinesterase at the neuromuscular junction have been observed [72, 74]. ECM and BM disruption appear to be major factors for these findings, as cartilage ECM and BM integrity has been found to be mainly interrupted in the cartilage, heart and brain tissue [67, 75]. Furthermore, perlecan has been shown to increase in osteoarthritic cartilage (Fig. 2), possibly due to regeneration efforts [23].

Collagen IV

Collagen IV is made up of 6 different alpha chains that can assemble into 3 different heterotrimers, $\alpha 1\alpha 1\alpha 2$(IV), $\alpha 3\alpha 4\alpha 5$(IV), or $\alpha 5\alpha 5\alpha 6$(IV) [27, 76]. These combined networks show a tissue-specific distribution (Fig. 3) and thereby define BM structure and function [77]. During development, collagen, which is an $\alpha 1\alpha 1\alpha 2$(IV) network, is ubiquitously distributed in BMs. During the maturation process, this network gets partially replaced, for example, by collagen $\alpha 3\alpha 4\alpha 5$(IV) in the glomeruli of the kidney, in the cochlea, eyes, testis and lung, and by collagen $\alpha 5\alpha 5\alpha 6$(IV) in the bowman′s capsule of the kidney, the skin, esophagus and smooth muscle cells [78] as well as in the human synovial lining of the knee joint [79].

The mechanical stability, as opposed to the assembly of BMs, is largely dependent on its collagen IV scaffold [77, 80]. Many different cells have been shown to bind to collagen IV including platelets, hepatocytes, keratinocytes, and endothelial, mesangial, and pancreatic cells, as well as diverse tumor cells [27]. These interactions are mediated by integrins and non-integrin receptors, which show a collagen IV chain-specific binding [27]. Integrins such as $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 3\beta 1$, $\alpha 6\beta 1$, $\alpha 10\beta 1$, $\alpha 11\beta 1$, $\alpha v\beta 3$, and $\alpha v\beta 5$ have been described [27], while non-integrin receptors such as CD44 [27] and discoidin domain receptor-1 (DDR-1) have been reported [81]. DDR-1-collagen IV interactions have been demonstrated to be important for the structural integrity and filtration function of the BMs in the kidney [82].

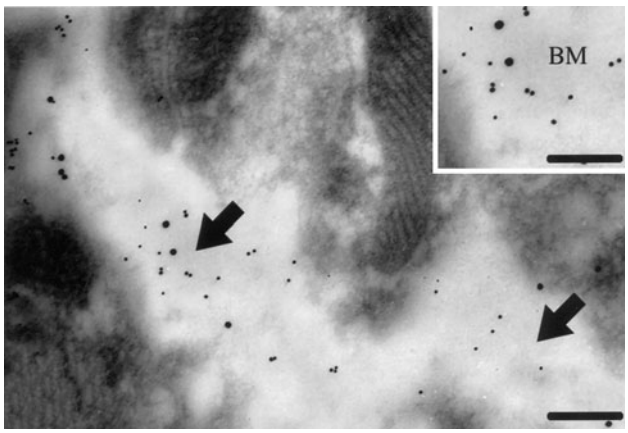

Fig. 3 The interconnected networks of laminin-111 (*large gold particles*) and collagen IV (*small gold particles*) is here shown in a basement membrane of the kidney. The *inset* shows a higher magnification. *BM* Basement membrane. (Taken from [201], with permission from the publisher)

It has been demonstrated that the proteolytic degradation or denaturation of collagen IV results in novel binding sites [83] that could further effect and alter integrin specificity and the biological functions of collagen IV [27]. This proteolytic cleavage, for example, was shown to support angiogenesis [84]. Furthermore, a proteolytic fragment of α3(IV), namely tumstatin, has anti-angiogenic activity and is discussed as a potential candidate for cancer therapy [85].

Notably, the α1(IV) and α2(IV) mutations are typically embryonic lethals [77]. However, in humans, mutations in the α1(IV) may not be lethal and can exhibit a phenotypic heterogeneity. A cerebrovascular disease, known as HANAC syndrome (hereditary angiopathy with nephropathy, aneurysm and muscle cramps), has been described [86]. Furthermore, neurological diseases such as encephaloclastic porencephaly or vascular diseases such as recurrent hemorrhagic stroke are associated with mutations in collagen α1(IV) [86]. Autoantibodies against the α3(IV) chain leads to Goodpasture syndrome, a rapidly progressive glomerulonephritis associated with lung hemorrhage [87]. In addition, α3(IV), α4(IV) or α5(IV) mutations cause Alport syndrome, which leads to renal failure, deafness and retinopathy in patients [27, 88, 89]. Stem cell therapies that could benefit Alport syndrome have just recently been described [90].

Nidogens

Nidogen-1/entactin-1 [91] and nidogen-2/entactin-2 [92] are BM glycoproteins. Structurally, they appear highly similar. Both nidogens consist of three globular domains that are separated by a link-like and a rod-like region [92, 93]. In addition, both are known to act with a wide range of BM proteins [30, 91, 92]. Nidogens are mainly expressed by mesenchymal cells and are deposited into the epithelial and endothelial BMs during development [94]. In skin tissue, fibroblasts have been described to be the source of nidogens [92, 95]. Nidogen-1 and nidogen-2 have been observed in the mesenchyme of different murine tissues during limb development [96] and have been shown to exist in the rib anlagen [97]. Furthermore, both nidogens have been described in murine and human adult articular cartilage [21, 22].

Due to their similar structure and affinity to comparable ECM proteins, nidogens are thought to have similar functions such that they are capable of compensating for each other [97]. Indeed, in nidogen-1 or nidogen-2 knockout mice, BM formation is not interrupted [98]. Furthermore, a compensatory process has been shown for nidogen-2 in nidogen-1 knockout mice (Fig. 4), especially in muscle and heart tissue [99]. Nidogen double-knockouts are smaller than their wild-type littermates [100], exhibit syndactyly, and some of these animals have more severe defects of the skeleton, such as hypoplasia [101]. A double knockout leads to perinatal death as a consequence of lung and heart anomalies and BM defects [100, 102]. Also, the capillary BMs were disrupted with an almost complete loss of laminin-411 and reduction of collagen IV and perlecan, thereby causing microhemorrhages of the skin. However, some BMs still develop without abnormalities, such as the dermal–epidermal junction [103].

Nidogens are able to interact with different receptors and nidogen-2 has an even more restricted tissue distribution (e.g., in muscle tissue) at the neuromuscular junction [104, 105] or in cartilage tissue (Fig. 5) [22]. While nidogen-1 integrins such as $\alpha v\beta 3$ and $\alpha 3\beta 1$ have been described [106, 107], interactions with these integrins could not be observed for nidogen-2 [22, 92]. Nidogen-1 knockout mice developed neurological defects, showed altered anionic charges in the glomerular BM, were observed to have structural alterations in the BMs of brain capillaries and the lens capsule and were characterized with impaired wound healing [108–111]. These finding indicate diverse functions of nidogens.

Due to their strong affinity to laminin and collagen IV, nidogens are considered to be link-proteins in some BMs [30]. In particular, the laminin γ1-nidogen-1 complex has been shown to be important during organ development [94, 112, 113]. Nidogens are highly sensitive to proteolytic cleavage; however, laminin γ1-binding can decrease this strong susceptibility to proteolysis as shown for nidogen-1 [113]. Moreover, the same protective effect has been reciprocally demonstrated [94], therefore the removal of nidogens might initialize BM disintegration. Furthermore, while they could be ideally suited for maintenance, they

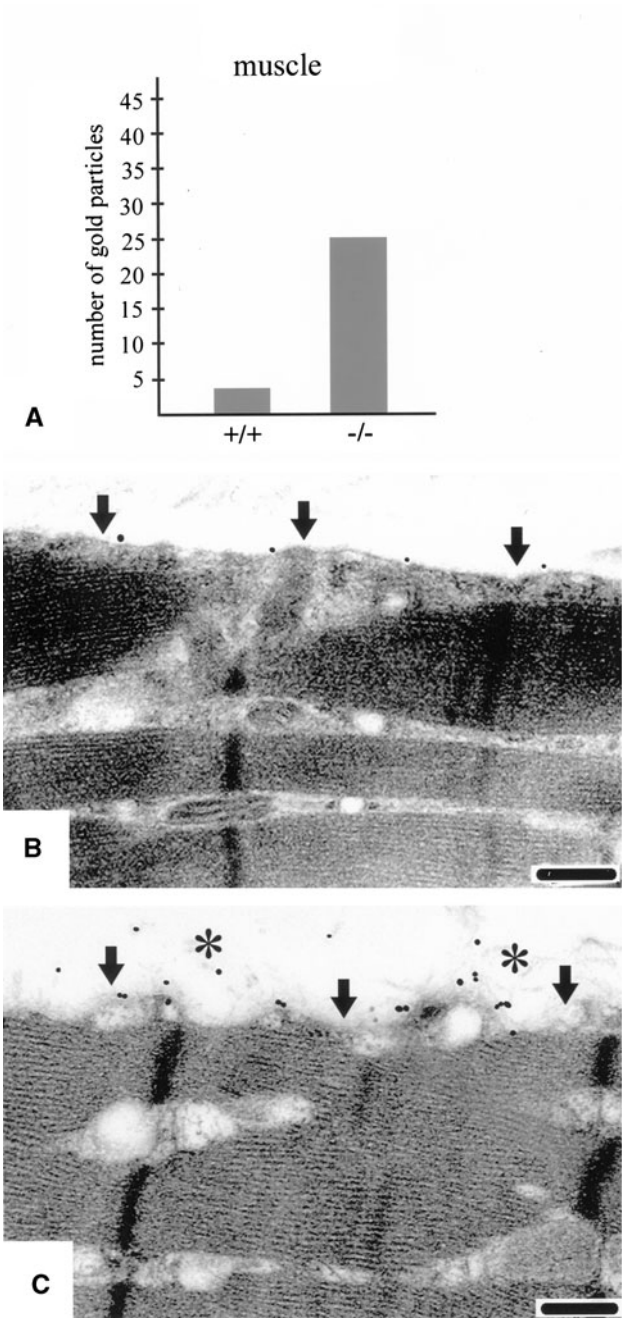

Fig. 4 More nidogen-2 is found in the BM of skeletal muscle in nidogen-1 knockout mice compared to control mice (**a**), sparse labeling of muscle BM of a control mouse (**b**), and a higher amount seen in a nidogen-1 knockout mouse (**c**). (Taken from [99], with permission from the publisher)

also may facilitate the fast remodeling of different matrices and might be early targets in tissue destruction pathways, such as metastasis [31]. Just recently, nidogen-2 has been observed to be strongly upregulated in the serum of patients with ovarian carcinoma and has been proposed as an additional cancer biomarker [114].

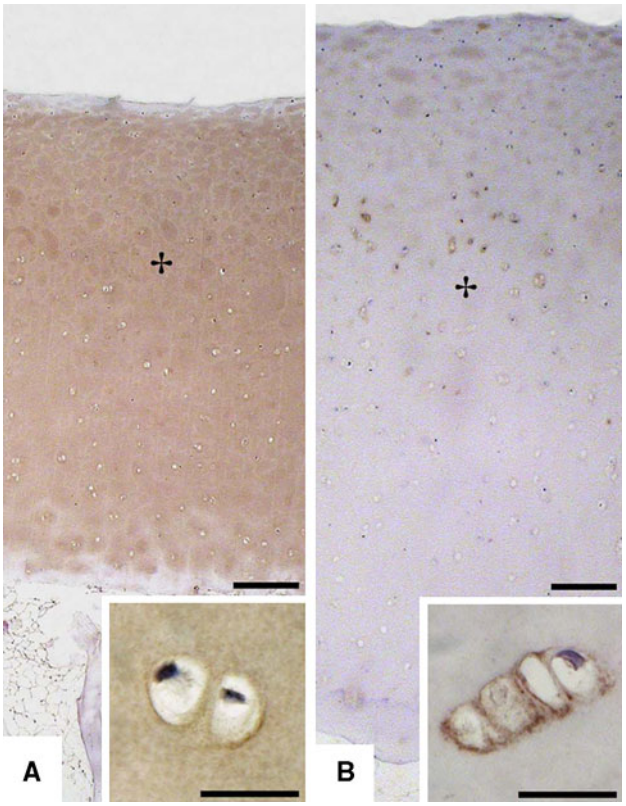

Fig. 5 Nidogen-2 (**b**) exhibits a more restricted tissue distribution in human articular cartilage than nidogen-1 (**a**). (Taken from [22], with permission from the publisher)

A stem cell's niche is its specialized ECM

Stem cells are important during development, regeneration and cancer development [115]. Embryonic stem cells (ESCs) are undifferentiated cells with the ability to develop into different tissues, whereas adult stem cells are thought to reside in specific tissues, with the possibility to regenerate the tissue if needed. Stem cells are embedded in a highly tissue-specific environment, which consists of an ECM with additional surrounding cells, such as organ-specific mesenchymal cells [15]. A stem cell niche is defined as a microenvironment that regulates the maintenance, self-renewal, activation, proliferation and long-term regenerative capacity of stem cells via external signals. The niche is, therefore, a key prerequisite for proper stem cell function and fate determination [15, 116, 117]. A single sECM, along with integrins, growth factors and diverse proteases are interconnected in complex pathways in stem cell niches. Stem cell niches are thought to be anatomically localized in protected sites of tissues [118]. Defining the composition of stem cell niches would help to understand the regulation of stem cells and to exploit their therapeutic potential [9]. Furthermore, knowledge about niches in different organs can help to elucidate the emergence of

diseases including diabetes, neurodegenerative diseases, cancer development and metastasis [60].

BMs are capable of governing cell fate by inducing signaling cascades, as well as stabilizing cellular structures. Thus, its components could potentially be used in stem cell and gene therapy approaches [119]. Over the last few years, there has been significant progress made in characterizing different stem cell compartments, such as the hematopoietic, epidermal, intestinal or neural stem cell niches [120–122]. Most niches contain a BM, to which stem cells attach [17]. The BMs are believed to have important functions for the structural integrity of stem cells [123]. They are also important for facilitating the polarization of cells, which is a prerequisite for proper symmetric and asymmetric cell division [61, 118, 124]. It has been suggested that, in contact with a BM, cells maintain their stemness, whereas cells that have detached from the BM undergo terminal differentiation [9].

Embryonic stem cells and their BM components

Human embryonic stem cells (hESCs) are seen by some as a potential source for therapeutic approaches, due to their indefinite proliferation in culture and ability to differentiate into various cell types [125]. Embryonic stem cells are colony-forming adherent and undifferentiated cells. Their adhesion mechanisms are important for their survival and differentiation and are thought to include a special ECM. Recently, it has been found that laminin-511 and nidogen-1 are expressed by human embryonic stem cells [126]. In addition, Lutheran-glycoprotein and its truncated form, basal cell adhesion molecule (B-CAM), which is a laminin-511-receptor, has been reported. Furthermore, adhesion of hESCs was driven by $\alpha 3\beta 1$ via laminin-511. Moreover, hESCs have been found to be positive for laminin-111 [127]. In vitro, single ESCs were able to reassemble into embryoid bodies with the aid of a laminin–nidogen–complex via $\alpha 6\beta 1$ integrin, subsequently differentiating into endodermal, ectodermal and mesodermal derivates, as well as hematoendothelial progenitors [126]. Mimicking stem cell niches as a fibrous scaffold with a BM texture has been shown to increase the expansion of hematopoietic and ESCs [128]. Proper BM formation seems to be involved in the maintenance of the differentiation status of BM-coupled cells such as in the myotome or the central nervous system [129, 130]. During development, BMs seem to have an inhibitory effect on the progression of cell differentiation [131]. Notably, other reports have found that hESCs retained their undifferentiated state if cultured on Matrigel® (includes mainly laminin-111), whereas hESCs underwent differentiation on substrates like fibronectin [132, 133].

BMs are important contributors during epithelial-mesenchymal-transition (EMT)

During development, undifferentiated cells in contact with BMs become polarized and as a consequence form the ectoderm [131]. Furthermore, using ESC-derived embryoid bodies (EBs), evidence demonstrates that unpolarized cells that fail to contact the BM undergo apoptosis, which leads to cavitations that create the proamniotic cavity [131, 134, 135].

Gastrulation, which leads to the formation of the mesoderm and endoderm, involves an event known as the epithelial-mesenchymal-transition (EMT). During this process, cells of the primitive ectoderm become activated by exogenous stimuli, followed by a loss of contact with the neighboring cells and the underlying BM that promotes the migration of cells into the space between the ectoderm and the extraembryonic endoderm [131]. Fujiwara et al. [131] proposed that the BM not only promotes the epithelialization of primitive ectoderm cells [135] but also promotes mesodermal differentiation by influencing the expression of genes important for mesodermal differentiation. In laminin $\gamma 1$ knockout mice, BM deposition did not occur, resulting in the failure of ectoderm formation [131]. Furthermore, the destabilization of collagen IV induced EMT in renal cell cultures [136].

For proper EMT, the cytoskeleton has to become reorganized to allow the cell to migrate. Therefore, cell-to-cell contacts have to be reduced, while cell-to-ECM interactions have to be increased. [137]. In the presence of a BM, the actin cytoskeleton accumulated at the apicolateral region of the polarized cells, whereas in its absence, actin was distributed evenly throughout the unpolarized cells. Therefore, BMs prevent EMT initiation by influencing the dynamics of the actin cytoskeleton and the assembly and disassembly of junctional complexes [131]. During EMT, laminin-332 gets downregulated, indicating a mechanism that is important for proper cell invasion. Furthermore, it has been shown that proteolytic fragments of the laminin $\gamma 2$ chain liberated by MT1-MMP or MMP2 can trigger cell migration, therefore one could speculate that these fragments are generated during EMT, thus promoting cell migration [138].

BMs and EMT: a link to metastasis

Finding candidate marker genes for EMT would also have implications in cancer diagnosis, prognosis, treatment [138], and metastasis [139, 140]. EMT-genes such as Snail2 and Twist2 are also upregulated during cancer progression [131, 141, 142]. Changes in protein expression that are indicative of EMT include the upregulation of vimentin and a reduction in the expression of E-cadherin

[9, 138]. Signaling pathways important for EMT induction include Wnt, TGFβ, Hedgehog, Notch, and NFkB. Notably, some external stimuli that affect EMT induction include collagen, fibronectin, EGF, and HGF [138]. Cells undergoing EMT show a reduced expression of BM components such as laminin-332, nidogens and collagen IV α1 and α2 chains in addition to increased expression of proteases, such as MMPs. In addition, these cells demonstrate elevated secretion of ECM molecules important for the proliferation and migration of compounds such as collagen I and fibronectin [138, 143, 144]. Metastatic cells indeed showed significantly decreased to no expression of diverse laminin subunits, collagen IV and α-dystroglycan compared to their non-metastatic counterparts [145–147]. In addition, during EMT, the downregulation of laminin α5 and the upregulation of laminin α4 have been observed, suggesting that tumor cells utilize laminin-411 due to their invasive behavior [148]. Furthermore, laminins and collagen IV are localized throughout the ECM of some cancer tissues [149, 150], indicating fragments of these proteins that are not able to self-assemble into BM structures. Laminin-332 fragments can improve cancer cell migration and, for this reason, it has been discussed as a potential target for cancer therapy [151, 152].

Depending on the stimulus, different MMPs are activated, such as cells activated by Ras that can upregulate MMP1. On the other hand, the activation of cells via HGF or Snail has been shown to activate MAPK signals, increasing the expression of MMP9 and MMP13 [138]. Furthermore, cell motility can be influenced by different integrin dependent pathways, including the Ras-Raf and MAPKinase or Rho- and Rac-controlled pathways [153, 154].

Adult stem cell niches: in vivo and in vitro

There is evidence that in different sites of the limbal compartment of the eye, various forms of typical BM components were localized, indicating that a different composition of ECM can regulate the phenotypic changes of the limbal cells and thereby regulate cell differentiation and migration via diverse cell-ECM-interactions [9]. The limbal stem cell compartment contains mostly collagen type IV α1 and α2, whereas collagen IV α5 and α6 chains were localized throughout the limbal and corneal BMs. Laminin-211 and -213 were most prominent and were shown to be specific for limbal BMs. While both nidogens and perlecan did not show any regional differences, laminin γ3 showed a specific immunoreactivity in the limbal stem cell compartment.

The stem cell niche in skin has been recently reviewed [61]. The BM itself provides proliferative stimuli through the use of laminin-332 that stimulates anchorage, signaling and migration via $\alpha6\beta1$ integrins at hemidesmosomes and $\alpha3\beta1$ at focal adhesions [155, 156]. Laminin-332 supports cell adhesion and migration more efficiently than other laminins, which is mainly mediated by integrins $\alpha3\beta1$, $\alpha6\beta1$ and $\alpha6\beta4$ [157]. It is important in skin and other epithelial tissues and it plays important roles in the stabilization of the epidermal-dermal-junction and in wound healing [157]. More specifically, it has been shown that the proliferation potential of such cells can be enhanced via exposure to $\beta1$-integrins [156], which induces focal adhesion tyrosine kinase and Src tyrosine kinase, thereby stimulating the Ras-MAPK pathway and inducing epidermal migration. Balancing these pathways is known to be important for homeostasis and cancer development [158]. Notch signaling is one of the key mediators for the differentiation or the repression of basal cells via the regulation of integrin levels [61]. Muffler et al. [117] demonstrated that an increase in MMPs (MMP1 by basal keratinocytes, MMP2 by dermal fibroblasts) led to the degradation of collagen IV, laminin-332 and -511, nidogen and integrins $\alpha6$ and $\beta1$, thereby altering the long-term differentiation potential of the epidermis, which is thought to be due to stem cell niche destruction. It has been further proposed that integrin-nidogen-laminin-332 complexes could be promising components for the regulation of the stem cell niche and epidermal maintenance [117]. In vitro, collagen IV can be used to enrich proliferative human skin keratinocytes, with high levels of integrin $\alpha6$ and $\beta1$ subunits [159]. The $\alpha6$ integrin subunit has been used for the isolation of human epidermal stem cells [160].

In the muscle stem cell niche [62, 161], it is suggested that the BM components regulate satellite cell behavior, as these cells lose their proliferative capacity in vitro, probably due to the loss of the BM components of its niche [162–164]. Several ECM molecules, including BM components, affect myoblast differentiation and proliferation [165, 166]. The influence of BMs on satellite cells has been previously reviewed in detail [62]. Laminins in skeletal muscle interact with cell surface receptors to initiate BM formation [167]. Furthermore, a muscle-specific isoform of laminin-211 [6] has been characterized in the stem cell compartment that connects cells via integrin $\alpha7\beta1$ and dystroglycan. Integrin $\alpha7\beta1$ is also upregulated during the regeneration of muscle tissue. Integrin $\alpha3$ plays a role in satellite cell migration and differentiation. Furthermore, the integrin $\beta1$ in muscle tissue is important in myoblast attachment in vitro [161, 168]. Laminins have been shown to give rise to additional yet smaller myotubes, whereas collagen type IV or Matrigel® resulted in thicker yet fewer myotubes. In addition, the stiffness of the surrounding ECM influences the proliferation rate of myoblasts, resulting in higher stiffness associated with increased proliferation [169]. Yao et al. [170] have described a

positive effect on myoblast migration through laminins via $\alpha 7\beta 1$ integrins.

The stem cell niche of cardiac tissue in vivo has not yet been described in detail; however, it is known that fetal heart tissue and adult cardiomyocytes secrete collagen IV and fibronectin [171]. It has been hypothesized that cardiac stem cells are quiescent cells, surrounded by a BM, and if activated give rise to cells of the transient amplifying pool that are responsible for tissue repair [172]. Laminins in particular are known to play an essential role in cardiac tissue development, as elucidated by laminin $\alpha 2$ and $\alpha 4$ mutations [173]. Furthermore, laminin $\alpha 4$ mutations were shown to also result in endothelial and cardiac cell alterations [58]. Interestingly, in heart tissue, BMs are primarily important for the control of ECM assembly and deposition, thereby indirectly influencing cell behavior. Malan et al. [174] have recently shown that a lack of laminin $\gamma 1$ and a corresponding lack of BMs are not essential for the development and differentiation of hESC into cardiomyocytes. However, they detected a clearly stronger deposition of several ECM proteins, e.g., collagen I, VI and fibronectin, which resulted in an altered spacing between the cells and indirectly caused a defective intercellular coupling via gap junctions resulting in altered propagation of electrical signals. Furthermore, increased amounts of the pacemaker-like cells were found, suggesting a compensatory mechanism to overcome the increased ECM depositions and the alterations in the propagations of electrical signals. These results could explain the pathophysiological development of cardiomyopathies where the deposition of ECM is one of the main causes for life-threatening arrhythmias [174, 175]. Moreover, collagen IV plays an important role in cardiac tissue and shows an increased deposition in the ECM after myocardial infarction (for review, see [176]). It has been proposed that ECM deposition in heart tissue could be repressed, either by changing the integrin pattern to a more laminin-binding pattern and less fibronectin-binding integrins ($\alpha 5\beta 1$, $\alpha v\beta 3$), which could accelerate maturation and reduce ECM secretion, or by co-injections of hESCs with extracellular matrix molecules [125].

A special kind of niche is the vascular niche, which is important for cellular and developmental processes, for differentiation and proliferation of the stem and progenitor cells, as well as for the development of cancer metastasis. The influence of the vascular niche in diverse diseases has been reviewed previously [60, 177]. Despite exhibiting highly variable features in different tissues, Nikolova et al. [60] suggested that a common feature of all the vascular niches is to provide a BM to cells that are unable to form their own. Furthermore, these cells are dependent on their vascular niche to retain a high degree of plasticity [60]. Cells that are included in this niche are the endothelial cells and the smooth muscle cells in the macrovasculature or the pericytes of the microvasculature. In vitro, endothelial cells have been shown to be supportive in the differentiation of pancreatic cells [178], in the stimulation of the neurogenesis of neural stem cells [179], and in supporting the proliferation of myoblasts [180]. Co-transplantations of hESC-cardiomyocytes with hESC-endothelial cells could improve the formation of functional capillaries and the secondarily blood supply [125]. Moreover, recent data present in vitro and in vivo evidence for the important role of pericytes–endothelial interactions to stimulate BM formation and thereby stabilize vascular tube formation [181]. Collagen IV promotes the differentiation potential of ESCs to endothelial cells [182]. Due to their stem cell characteristics and their ability to produce BM components, pericytes are thought to be important for the function of the blood–brain barrier [183, 184]. Furthermore, pericytes enhance the low-tissue regeneration and proliferation capacity of epithelial cells by influencing the ECM microenvironment. Pericytes are a source of laminin $\alpha 3$ and $\alpha 5$, collagen IV $\alpha 1$ and $\alpha 2$ chains, integrin $\alpha 7$, and integrin $\alpha 1$ in human skin [184]. In organotypic cocultures, it has been found that they enhanced the deposition of laminin-511/521 in the dermal-epidermal junction. These observations could be used for the ex vivo expansion of epidermal progenitors to treat skin defects [184]. In muscle tissue, a loss of capillaries leads to a loss of satellite cells, which is thought to result from an interaction of endothelial cells with satellite cells [180]. Furthermore, pericytes are able to differentiate into mesenchymal lineage cells [185]. Therefore, pericytes could also be a possible stem cell source in muscle tissue that would be able to differentiate into myoblasts. Changes in the BM composition and/or its destruction in vascular tissues could be important in different diseases, including multiple sclerosis or for diseases of the pancreas in the context of islet cell transplantation or autoimmune insulitis [123].

Improvement of culture conditions for adult stem cells

It has been proposed that stem cells require an authentic equivalent of their in vivo environment, rather than an artificial surrogate, such as collagen type I [117]. Muffler et al. [117] demonstrated a high regenerative capacity of human epidermal stem cells in scaffold organotypic cultures (OTCs) rather than in OTCs made up of collagen type I. The imitation of different tissue-specific ECMs can promote cell differentiation and proliferation in vitro [186], as has been shown, for example, by de-cellularized matrices of tissues, which were sufficient for the differentiation of stem cells into the cells and structures indicative of the respective tissue [187].

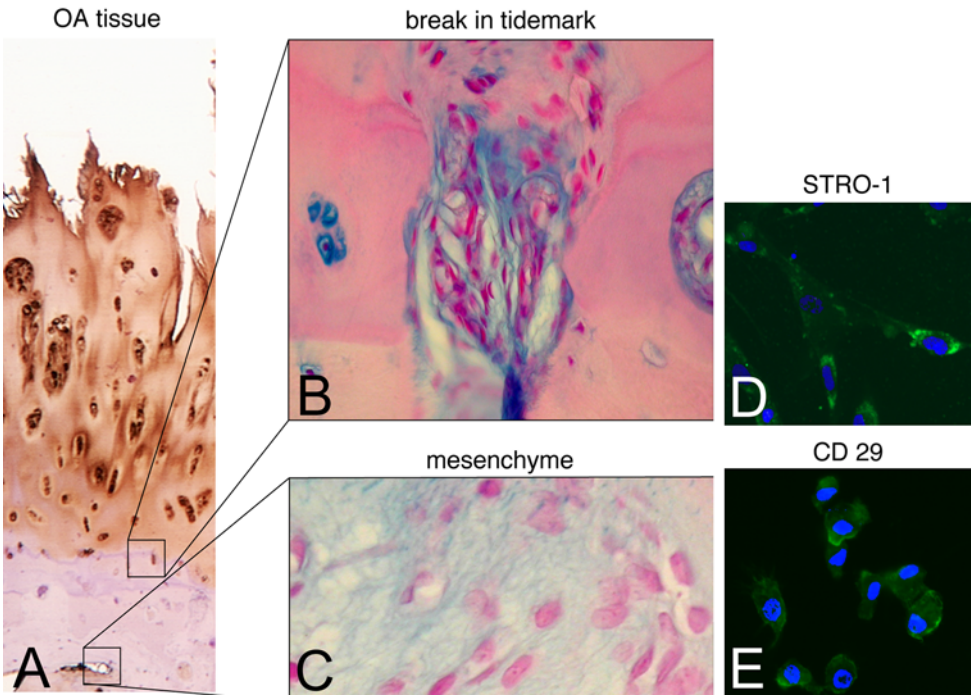

Fig. 6 Tissue from late stages of osteoarthritis exhibits brakes in the tidemark (**a**) through these mesenchymal cells and blood vessels enter the cartilage tissue (**b**), perhaps bring in stem cells from the mesenchyme underneath (**c**). The progenitor cells are positive for STRO-1 (**d**) and CD29 (**e**), two so-called stem cell marker. (Taken from [199], with permission from the publisher)

Adult mesenchymal stem cells and tissue engineering?

Mesenchymal stem cells (MSCs) could be a good starting point for tissue engineering approaches, as they have been shown to be multipotent cells with self-renewal abilities and a potential to differentiate into a variety of cell types [188, 189]. MSCs are proposed to be directed to the sites of injury [190], suggesting them as a starting point to initiate regeneration [191, 192]. The observation that systemically delivered MSCs can integrate into a perivascular/intramural location has been shown by Toma et al. [192], indicating that perivascular tissues could function as a reservoir of tissue-specific regenerative cells [192]. It has been proposed that pericytes are a type of MSC and vice versa, due to their similarities [184, 186]. Potapova et al. [193] found that endothelial cell migration, invasion through BMs, proliferation and survival can be supported by MSCs. Furthermore, MSCs can be differentiated into vascular cell types [186], whereas pericytes are able to be differentiated into mesenchymal lineages such as chondrocytes, adipocytes and osteocytes [184].

Effect of BM components on adult MSCs

The imitation of bone marrow cell-derived ECM (including laminin, perlecan, fibronectin, collagen I) in vitro has resulted in a complete bone-like structure in vivo that contained hematopoietic marrow with adipocytes and stromal cells that supported hematopoiesis and osteoclastogenesis [194], suggesting that marrow-derived ECM provides important micro-environmental cues in vivo and preserves the stem cell properties of MSCs [194]. ESCs could be differentiated into smooth muscle cells (SMCs) via collagen IV [195], whereas bone marrow-derived MSCs significantly increased their proliferation rate [188, 196]. Collagen IV positively influenced the proliferation of human bone marrow-derived MSCs, whereas laminin-111-coating enhanced the smooth muscle cell differentiation marker expression [188].

It has been indicated that laminin-332 plays a suppressive role in chondrogenic differentiation of mouse embryonal carcinoma-derived chondroprogenitor cell lines [157]. Additionally rat periosteum, as well as human MSCs, express laminin-332, which induces osteogenic differentiation via an ERK signaling pathway [157, 197] suggesting a possible role for laminin-332 during bone development [157]. Laminin-332 has growth-stimulating activity depending on the type of target cell [49]. The soluble form of laminin-332 stimulated growth of MSCs via $\alpha 6\beta 1$ integrin, thereby inhibiting chondrogenic differentiation. Moreover, laminin-332 promoted attachment and spreading of MSCs in vitro [157]. The suppression to one cell lineage by laminin-332 may favor the commitment of MSCs to other cell lineages (adipocytes or myoblasts) as proposed by Hashimoto et al. [157].

Perlecan might improve the bioavailability of diverse growth factors in vitro to increase the proliferation and differentiation potential of MSCs. BMPs and TGFβs are widely used in vitro to improve chondrogenesis [198] and for mesenchymal stem cell-like cells from human osteoarthritis (Fig. 6) as described recently [199].

Conclusion

Understanding of the structure and components of the human BMs in different tissues would have important implications for the development of more physiologically relevant conditions for the optimized cell growth and differentiation of cell lines in vitro, due to the importance of environment in maintaining specific cell properties in vitro.

Mimicking a tissue-specific stem cell niche will help facilitate stem cell self-renewal and create a controlled differentiation ex vivo environment. The identification of specific niche parameters of diverse tissue types in vivo will not only help to understand stem and progenitor cell regulation but will also further improve their enrichment and in vitro expansion for cell biologically relevant therapeutic strategies. It has been shown that BM components could be used to create an in vivo-situation for maintaining stem cell properties and that they are a useful tool in tissue engineering techniques. The receptor expression pattern of integrins, for example, and their signaling pathways in hESC and adult stem cells requires further investigation to produce a better understanding of how stem cells modulate their specific environment to create optimal niche conditions. Further work is needed to understand the complex microenvironments created mainly by BM components of different tissues, their stem cells and progenitors during homeostasis, diseases and repair.

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